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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,776	03/29/2004	David F. Muir	UF-336XC3D1	4996

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GOODWIN PROCTER LLP
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BOSTON, MA 02109-2881

EXAMINER

AFREMOVA, VERA

ART UNIT	PAPER NUMBER
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1657

MAIL DATE	DELIVERY MODE
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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/812,776	Applicant(s) MUIR, DAVID F.	
	Examiner Vera Afremova	Art Unit 1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/20/2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6-23,30-40,42-56 and 117-123 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,6-23,30-40,42-56 and 117-123 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/20/2007 has been entered.

Claims 1, 6-23, 30-40, 42-56 and 117-123 as amended (2/20/2007) are pending and under examination.

Claims 2-5, 24-29, 41 and 57-116 are canceled by applicant.

Claim Rejections - 35 USC § 112

Claims 1, 6-23, 30-40, 42-56 and 117-123 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 38 recite “untreated” nerve graft (line 7) in the method of preparing a nerve graft by *in vitro* culturing, thus, raising uncertainty about what treatment agent might be intended during *in vitro* culturing as claimed. The limitations such as “degrading CSPG” and “enhancing post-implantation” are the intended effects of “in vitro culturing” as claimed. The culturing step is generic as claimed. No treatment agent/step is recited in the claims. Thus, it is uncertain what treatment is encompassed in the method for preparing a nerve graft by negative recitation about some “untreated” nerve.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 6-15, 17-21, 30-40, 42-51, 53-56 and 117-120, 122 and 123 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by La Fleur et al. (IDS reference; J. Exp. Med. 1996, 184:2311-2326) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein method comprises 1) step of culturing the nerve tissue segment *in vitro* and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and DMEM medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue.

The reference by La Fleur et al. discloses a method for treating mammalian nerve tissue wherein method comprises 1) step of “culturing” the nerve tissue in vitro in DMEM medium comprising various supplements at temperature 37°C for various periods of time including 12, 24 and 2) step of “killing” the nerve tissue by chemical treatment for further extraction of proteins, RNA and other components (page 2312, column 2, par. 1-2). The nerve tissues or nerve segments are held or adhered to plastic dishes and, thus, combined with a generic adhesive. The nerve tissues derived from sciatic nerves that connected to both central and peripheral nervous system tissues.

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The cited reference comprises identical active steps of culturing and killing nerve tissues under conditions as presently claimed. Thus, the cited reference anticipates the claimed invention.

2. Claims 1, 6-15, 17-23, 30-40, 42-56 and 117-123 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Lassner et al. (IDS reference; J. Reconstruct. Microsurg. 1995, 11 (6): 447-453) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue *in vitro* and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and DMEM medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by freezing. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays *in vitro* and *in vivo*.

The reference by Lassner et al. discloses a method for preparing a nerve tissue for use as a nerve graft wherein method comprises 1) step of culturing the nerve tissue segments *in vitro* under culture conditions including temperature permissive for cellular outgrowth or 37°C, time 48 hours and DMEM medium with serum, and 2) step of killing the nerve tissue by freezing at minus 18°C; for example: see page 448, column 2, last paragraph that relates to the second series of experiments. The nerve tissues or nerve segments are held or adhered to plastic dishes and, thus, combined with a generic adhesive. The nerve tissues derived from sciatic nerves that connected to both central and peripheral nervous system tissues. The cited reference also

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describes neurite outgrowth assays *in vitro* (figures 5 and 7) and *in vivo* regeneration upon reimplantation (page 449, col. 1).

The cited reference comprises identical active steps of culturing and killing nerve tissues under conditions as presently claimed. Thus, the cited reference anticipates the claimed invention.

3. Claims 1, 6-15, 17-21, 30-32, 34-40, 42-45, 47-51, 53-56, 119, 122 and 123 as amended remain/are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,448,076 (Dennis et al) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue *in vitro* and 2) step of killing the nerve tissue. Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and a medium. Some claims are further drawn to the nerve tissues being mammalian or rodent tissues. Some claims are further drawn to killing by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays *in vitro* and *in vivo*.

US 6,448,076 discloses a method for preparing a nerve tissue for use as a nerve graft (entire document including abstract) wherein the method comprises step of culturing *in vitro* the nerve graft in a medium or in a balanced salt solution (col. 3, lines 45-46), step of rendering the nerve graft acellular by chemical treatment (col. 3, lines 47-67 and col. 4, lines 26). The nerve graft is a mammalian peripheral nerve segment (col. 3, line 42). The cited patent discloses the 24-96 hours as time intervals for culturing/treating steps and the same temperature ranges

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including room temperature as required by the presently claimed method. Thus, the cited patent US 6,448,076 appears to teach the same active steps and the same structural elements in the method of making graft as claimed. The acellular nerve grafts were used to repair nerve gap in vivo (col. 4, lines 47-60) and results were evaluated in vitro (col. 5, lines 53-66). The cited patent US 6,448,076 teaches that the nerve graft made supported axonal regeneration and allowed for end-organ reinnervation (col. 6, line 21-24) and, thus, enhanced post-implantation traversal of an interface between the nerve graft and host tissue within the meaning of the claims.

Therefore, US 6,448,076 anticipates the presently claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 6-23, 30-40, 42-56 and 117-123 as amended remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,448,076 (Dennis et al), La Fleur et al. (IDS reference; J. Exp. Med. 1996, 184:2311-2326), Ide et al. (IDS reference; "Schwann cell basal lamina and nerve regeneration". Brain Research. 1983, 288:61-75) and Evans et al. (IDS reference; Progress in Neurobiology, 1994. Vol. 43, pages 187-233) as explained in the prior office action.

Claims are directed to a method for preparing a nerve tissue graft wherein the method comprises 1) step of culturing the nerve tissue *in vitro* and 2) step of killing the nerve tissue.

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Some claims are further drawn to culture conditions including time 24-96 hours, temperature 10°C to 37°C and a medium. Some claims are further drawn to the nerve tissues being mammalian including rodent and human. Some claims are further drawn to step of killing by freezing or by chemical treatment. Some claims are further drawn to adding a generic adhesive to the nerve tissue. Some claims are further drawn to additional step of performing neurite outgrowth assays in vitro and in vivo.

US 6,448,076 (Dennis et al) is relied upon for disclosure of a method for preparing a nerve tissue graft as intended for implantation (entire document including abstract) wherein the method encompasses steps of *in vitro* culturing and/or *in vitro* treating the nerve graft and step of rendering the nerve graft acellular by killing.

In particular, the cited patent US 6,448,076 (Dennis et al) discloses a chemical treatment for making acellular nerve grafts and lacks explicit teaching about rendering nerve graft acellular through killing by freezing. However, Evans et al. teaches freezing and thawing of nerve grafts for making the nerve grafts acellular and non-immunogenic (page 212, col. 2, last par.). The cited reference by Ide et al teaches that basal laminae of Schwann cells rather than living cells play important role in nerve regeneration after implantation of nerve graft (page 62, col. 1, par. 1).

The cited patent US 6,448,076 (Dennis et al) teaches the use of balanced salt solution and dubelco' modified base solutions for graft pre-treatment before acellularization but it lacks an explicit teaching about the use of an enriched culture media. However, La Fleur reference teaches that incubation of nerve segments in culture medium supplemented with cytokines

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results in up regulation of TIMP-1 expression and that TIMP-1 protects basement membrane of nerve tissue from uncontrolled disintegration or degradation after injury (abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute a supplemented culture medium for a buffered salt solution in two-step method of US 6,448,076 (Dennis et al) with a reasonable expectation in success in making nerve tissues as intended for nerve grafts because culturing nerve tissues promotes up-regulation of compounds that remodel basement membrane of nerve tissues and protect from uncontrolled degradation after injury as adequately taught by La Fleur et al.

One of skill in the art would have been motivated to kill the nerve graft living tissues in order to avoid tissue rejection upon transplantation as clearly taught by Evans et al. Killing by chemical treatment and killing by freezing are considered to be substitution of equivalents.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 2/20/2007 have been fully considered but they are not found persuasive.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by La Fleur et al. applicants argue that the cited reference relates to effects that are essentially opposite of the claimed invention since the claimed method recites a degradation of GSPG by "culturing"

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a nerve segment but La Fleur teaches that TIMP-1 (inhibitor of MMP) protects basement membrane from MMP during degeneration (response pages 8-9). Arguments are not found persuasive because the cited reference discloses method for making a nerve tissue segment or nerve tissue graft that comprises identical active steps such as 1) step of generic “culturing” a nerve tissue segment *in vitro* and 2) step of killing the nerve tissue. The claimed culture conditions are either generic (claim 1) or the claimed culture conditions including temperature, time and medium (claim 38, for example) are the same as recited for a culturing step in the cited reference. Thus, the intended final effects including “degrading CSPG” and “enhancing post-implantation” for remodeling/modifying nerve tissue segments cultured *in vitro* would be the same due to the use of identical “culturing” conditions. Moreover, the cited reference clearly acknowledges MMP as an inherent mediator of degradation of ECM components (page 2312, par. 2, for example) and it teaches that both MMP and its inhibitor TIMP are involved in remodeling nerve tissues.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 6,448,076 (Dennis et al) applicants argue (response pages 9-11) that Dennis does not recite the presently claimed effects including “degrading CSPG” and “enhancing post-implantation” and it rather relates to preservation of basal lamina. Yet, the final effects with regard to remodeling nerve tissue segment *in vitro* are considered to be the same as result of the same active steps of “*in vitro* culturing”. The claimed “*in vitro* culturing” is either generic (claim 1) or the claimed “*in vitro* culturing” encompasses the same temperature, time and medium (claim 38, for example) as in the cited patent.

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In response to applicant's argument it is also noted that a recitation of the intended use or effects of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, the nerve grafts made by the cited method were implanted and provided for axonal regeneration in vivo (col. 6, line 24).

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by Lassner et al. applicants argue (response page 11-12) that the method of the cited reference involved a cold storage at 4 degree C. However, the cited reference also discloses a second series of experiments that involve steps of culturing in DMEM and subsequent freezing as explained above. Applicants appear to argue that the second series of experiments disclosed by Lassner are intended for histological evaluation. Yet, the active steps are identical as required by the claimed method and the culture conditions are the same within the broadest reasonable meaning of the claims.

With regard to the claim rejection under 35 U.S.C. 103 applicants appear argue (page 19) that there is no suggestion to combine cited references. However, the cited references are in the same field of endeavor such as method of making nerve grafts intended for repairing nerve damage in vivo and they seek to solve the same problems as the instant application and claims such as provide for nerve grafts intended for nerve damage repair in vivo, and one of skill in the

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art is free to select components available in the prior art, *In re Winslow*, 151 USPQ 48 (CCPA, 1966).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

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May 8, 2007



VERA AFREMOVA

PRIMARY EXAMINER